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Role of topical tretinoin in melanoma and dysplastic nevi

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The retinoids have been investigated extensively as chemopreventive and therapeutic agents in a variety of neoplasms. They have been shown to inhibit the proliferation of transformed cell lines in vitro and transplanted tumors in vivo. In cultured murine melanoma cells, retinoids inhibit proliferation and induce differentiation. Human melanoma cell lines have shown a mixed response. The clinical experience with retinoids in melanoma has been limited. Previously we investigated the activity of topical B-all-*trans*-retinoic acid (Retin-A, vitamin A acid, retinoic acid, and tretinoin) against intracutaneous metastases from malignant melanoma. We saw complete remission of multiple lesions in one individual and regression of several lesions in a second patient. This experience led us to conduct the present pilot trial of topical tretinoin in dysplastic nevus syndrome. The latter is a precursor of malignant melanoma. We saw regression of some of the treated lesions to benign nevi showing minimal or no dysplasia. Thus topical tretinoin appears to possess some activity against melanoma and at least one of its precursor conditions. In view of these preliminary results, more extensive trials are warranted to better define the role of tretinoin in the chemoprevention of malignant melanoma in high-risk lesions. (J AM ACAD DERMATOL 15:822-825, 1986.)

The effects of the retinoids on dysplastic and neoplastic cells have been widely studied in vitro, in vivo, and in humans. They can be divided into cytotoxic and tumor-suppressive effects.[1-3] The cytotoxic effects cause tumor regression by direct killing of malignant cells, in the manner of classic antitumor chemotherapy. The tumor-suppressive or chemopreventive effects are those that inhibit the development of preneoplastic cells into the malignant phenotype. In the retinoids the tumor-suppressive effects are independent of the agent triggering the neoplastic process.[4]

In cultured murine melanoma cells, both of these kinds of effects are observed.[2,3,5-7] In vivo, topical tretinoin (retinoic acid and Retin-A) retards the growth of transplanted murine melanomas in a dose-dependent fashion.[8] The drug inhibits the proliferation of melanoma cells and promotes their development into mature melanocytes.[5]

The response of human melanoma cell to Retin-A in vitro has been mixed.[6,9,10] Some cell lines are inhibited but others show no response, and growth is even stimulated in some. We have seen marked heterogeneity from patient to patient in the response to Retin-A of melanoma cells from biopsy specimens, using a soft-agar colony-forming assay.[9] Results ranged from substantial inhibition of melanoma-colony formation to no effect at all. We have also demonstrated retinoid inhibition of human melanoma cells in a standard cell culture system.[10]

The clinical experience with retinoids in melanoma has been limited. We noted a response in

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three of 20 patients with metastatic melanoma treated systemically with 13-*cis*-retinoic acid.[11] Previously we treated two patients with topical tretinoin for intracutaneous metastases of malignant melanoma. In one of these patients there was complete remission of the treated lesions. In the other there was a partial response.[12]

The first patient was a 54-year-old man with 21 intracutaneous metastases to his axillae. He was treated with topical 0.05% tretinoin cream under Blenderm occlusive tape. Perilesional erythema was noted during treatment. After 1 month all the lesions had flattened to nonpalpable, blue-purple macules of the same diameter as the original papules.

Four of the treated lesions were biopsied and in all instances regression had occurred. Biopsy specimens showed dermal extracellular and intracellular melanosis with no evidence of tumor cells. The patient died 24 months later of visceral disease, but no new skin lesions became evident nor had the old lesions changed.

The second patient was a 59-year-old woman with widespread intracutaneous metastases over the right biceps. Numerous chemotherapies had been unable to control her aggressive local disease. There was no evidence of systemic metastatic disease and she was treated with topical tretinoin cream, 0.05%, under Blenderm occlusive dressing. Of the 22 lesions we treated, three appeared to respond clinically. Biopsy specimens from two regressing lesions were taken and no evidence of melanoma was noted. These results suggest that topical retinoid may be capable of controlling melanoma when administered to high local concentrations. Our experience with these two patients, together with tretinoin's demonstrated chemopreventive activity in vitro and in vivo, led us to conduct the preliminary trial reported here of topical tretinoin in the dysplastic nevus syndrome.

TOPICAL RETINOIC ACID THERAPY FOR MULTIPLE DYSPLASTIC NEVI

The dysplastic nevus syndrome is a recently characterized entity[13,14] that produces tan, brown, or reddish-brown macules or flat papules that on histologic examination demonstrate dysplastic melanocytic changes in a nevocellular nevus. These lesions may number from 1 to greater than 100. Their shape is irregular and often large (5 mm). They usually appear first at about the time of puberty, but new dysplastic nevi may develop throughout life. Both a familial type[15] and a more common sporadic[16] type have been described. They have identical histologic features.

These nevi may often be precursors to melanoma but it has been difficult to predict which dysplastic nevi will evolve to malignant tumors.[17] Therapeutic strategies that might eradicate these preneoplastic lesions before malignant transformation could avert significant morbidity and death. In patients with only a few lesions, this can be accomplished by surgical excision. Surgery is impractical and may be unacceptable to patients with many lesions, however. Furthermore, it has no value in preventing melanomas that arise de novo in previously normal skin. Currently the most common approach is to follow the nevi closely with serial clinical photographs and excise those showing melanoma's clinical changes.[18] Although the topical application of fluorouracil[19] may be an alternative, responses to its use have been erratic.

Recognizing that melanocytes from nevi may well be regulated differently than melanoma cells, we treated multiple dysplastic nevi in three patients with topical tretinoin in an effort to exploit the potential cancer-chemopreventive effects of retinoids.

Subjects and protocol

Patient A, a 58-year-old white man, was evaluated at the University of Arizona Health Sciences Center after removal of a cutaneous melanoma. He had no known family history of melanoma or dysplastic nevi. Examination of this patient's skin revealed a poorly demarcated 1 cm red plaque with flecks of blue pigment on the right shoulder. Distributed over the trunk were numerous 0.5 to 1.5 cm irregular, barely palpable, tan-red papules. Before beginning our experimental protocol, the patient's shoulder lesion was excised and found to be melanoma in situ.

Patient B, a 17-year-old white boy, was referred for evaluation of abnormal-appearing nevi. His mother had a history of cutaneous melanoma. His sister had dysplastic nevus syndrome. On examination there were found numerous, irregular, red-brown macules with uneven pigmentation. Most were 0.5 to 1.0 cm in diameter.

Patient C was a 46-year-old white man who had undergone excision of four cutaneous melanomas during the previous year. His brother had a similar history of cutaneous melanoma. The patient displayed numerous large, poorly marginated macules and papules whose color varied from red-brown to faint red.

Before therapy, each patient had had at least three diagnostic skin biopsy specimens representative of dysplastic nevi. Small portions of the lesions were removed to confirm the diagnosis histologically. A portion of each lesion remained for treatment. After informed consent was obtained, all three patients were treated with a 0.05% solution of tretinoin cream applied daily to individual lesions. A number of biopsied lesions, clinically characteristic of dysplastic nevi, were treated. These we covered with Blenderm occlusive tape, which remained in place until the next retinoid application.

Patient A was treated at home daily for 12 weeks. At the end of that time, biopsies of portions of three previously biopsied lesions were performed. Four months later, and again 3 months after that, additional skin specimens were taken from the same lesions.

Patient B received daily treatment at home for 10 weeks. This patient's therapy was discontinued 2 weeks early when he entered college. Repeat biopsies of three treated sites were performed after 10 weeks.

In our clinic, topical tretinoin was applied to patient C for 5 days each week for 12 weeks. Subtotal biopsies were performed on four of the treated nevi. Three months and 8 months after treatment, repeat biopsies were performed on these lesions. As was true of the first two subjects, the only treatment side effects patient C had were mild pruritus and erythema at the site of treatment.

Each biopsy specimen was interpreted at the University of Arizona Health Sciences Center by a staff pathologist and a dermatologist who were unaware of the nature of our experiment protocol. The following histologic criteria were the basis for diagnosis of dysplastic nevi: (1) junctional melanocytic proliferation in large nests, with absent to minimal cellular atypia; (2) downward proliferation and bridging of rete ridges; (3) spread of single large melanocytes along the basal layer; and (4) dermal lymphocytic and mesenchymal response. The concurrent presence of all criteria was not required for diagnosis of dysplastic nevus.[20]

RESULTS

At the end of treatment, some treated lesions had lost their red hues and were more uniformly brown, but most of the lesions showed only minimal changes in clinical appearance. Nevertheless, striking histologic changes were noted after treatment. Pretreatment skin biopsy specimens of clinically dysplastic nevi from our three patients all showed the characteristic histologic features of dysplastic nevi. Multiple-step sections through the posttherapy biopsies showed benign compound nevi without dysplasia in patients A and C, whereas all three posttreatment biopsies in patient B were interpreted as benign compound nevi with minimal dysplastic change. In patients A and C, skin biopsy specimens were taken from treated lesions several months after treatment. All continued to show changes of benign nevocellular nevi without dysplasia.

DISCUSSION

Three patients with multiple dysplastic nevi were treated with topical retinoic acid. All lesions biopsied after treatment and again several months later demonstrated features of either benign compound nevi with no dysplastic changes or only minimal residual dysplasia.

These preliminary results from a limited study are encouraging and call for more extensive trials of the use of topical tretinoin to resolve the dysplastic nevus syndrome. An agent effective in this role would have considerable value in the chemoprevention of melanoma. Unfortunately, this study's design allows for alternative interpretations of the results. It may be that the benign appearance of the posttreatment biopsy specimens was a sampling artifact. Since dysplastic nevi often have only focal melanocytic dysplasia, the posttreatment biopsy specimens conceivably may have represented areas of benign nevus. It is also possible that the inflammation caused by the pretreatment biopsy could have induced resolution of the dysplastic changes independently of retinoid therapy.

In related work, early results from a carefully designed trial of systemic 13-*cis*-retinoic acid suggest that this retinoid neither suppresses nor reverses dysplastic nevi.[21]

It is important to pursue the study of the retinoids in this and other preneoplastic conditions, since this class of drugs may have great potential for cancer chemoprevention. The development of

relevant in vitro screening systems for the evaluation of drug effects should be a high priority.

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